EXHIBIT B

IN THE UNITED STATES DISTRICT COURT

FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA

CHARLESTON DIVISION

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION	**Master File No. 2:12-MD-02327** **MDL 2327**
THIS DOCUMENT RELATES TO: **Wave 4 Cases**	**JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**

Expert Report of Harvey Winkler, MD

Regarding Gynemesh PS and Prolift

Qualifications: Background and Education:

I am currently the Co-Chief of Female Pelvic Medicine and Reconstructive Surgery (FPMRS) at the Northwell Health System in Long Island, New York and an Associate Professor at the Hofstra Northwell School of Medicine. I am also the Program Director of the fellowship training program in FPMRS at the Hofstra Northwell School of Medicine. Board certified in Obstetrics and Gynecology and Female Pelvic Medicine and Reconstructive Surgery by the American Board of Obstetrics and Gynecology, I am licensed to practice medicine in the State of New York. Additionally, I have an Illinois license (inactive, as I currently do not practice in that state). Pending approval, I will have an Australian medical license to consult and instruct physicians on surgical procedures, internationally.

I began medical school in 1988, at the age of 20, and graduated from the Albert Einstein College of Medicine in 1992. After which I started my residency in Obstetrics and Gynecology at

Montefiore Medical Center under the auspices of the Albert Einstein College of Medicine, from July 1992 to June 1996. In July of 1996 I began my fellowship in Urogynecology under the tutelage of Dr. Peter Sand, an internationally renowned Urogynecologist, at Evanston Hospital, which was then affiliated with Northwestern University. I completed the fellowship in June, 1998. In July 1998, I launched the Urogynecology Division at Maimonides Medical Center and was appointed the Chief of the Division where I developed the division into a local center of excellence.

In May of 2002, I resigned from Maimonides and moved to North Shore LIJ which is now known as Northwell Health. In 2006 I was appointed the Co-Chief of the Division of Urogynecology: Female Pelvic Medicine and Reconstructive Surgery. In July of 2008 the Fellowship program, which I pioneered and assembled, in Female Pelvic Medicine & Reconstructive Surgery commenced and I was appointed the Program Director. I was responsible for attaining credentialing for the program and received such from the American Board of Obstetrics and Gynecology (ABOG) in 2011 and from the Accreditation Council of Graduate Medical Education (ACGME) in January 2013 retroactive to July 2012. The Fellowship program in FPMRS at the Hofstra Northwell School of Medicine is one of only 50 programs in the country currently approved by the ACGME.

I am currently a member of the American Urogynecologic Society (AUGS), International Urogynecological Association (IUGA), American College of Obstetricians and Gynecologists (ACOG), New York Obstetrical Society, (NYOB), American Association of Gynecological Laparoscopists (AAGL), and the American Institute of Minimally Invasive Surgery, (AIMIS). I have previously served as a member of the AUGS Public Relations Committee.

Throughout my career, I have championed the education of residents and fellows, training them to be future caretakers, pioneers, and leaders in women's health. I am responsible for the resident education curriculum and rotations in Urogynecology at North Shore University Hospital and Long Island Jewish Medical Center. In June of 2012 I was awarded the APGO Excellence in

Teaching Award for resident education. As Program Director for the Fellowship Program in FPMRS I am responsible for ensuring that the fellows receive a superior education, which includes but is not limited to: organizing the didactic lecture series, presenting lectures, journal clubs, morbidity and mortality conferences, and one-on-one surgical training of multiple urogynecologic procedures. Furthering my role in graduate education, I am a member of the Faculty Council of the Hofstra Northwell Scholl of Medicine as well as member of the Northwell Health Graduate Education committee.

I have also trained physicians on the techniques, patient selection, risks and complications of abdominal sacral colpopexy and transvaginal mesh. I have travelled nationally to educate these physicians and am scheduled to do such internationally in Australia in March 2017. Furthermore, I have been invited to lecture at the Urogynecological Society of Australia annual meeting in Melbourne in March of this year.

As part of my dedication to education and requisite for continuous learning for myself in all aspects of health care, I am currently enrolled in an MBA program focusing on Health Services Management at the Frank. G. Zarb School of Business at Hofstra University. I am planning to complete the program in 3 years despite working full time, and currently have a GPA of 4.0.

Throughout my career, I have always championed women's health through knowledge, research and innovation, with the goal of quality of life improvement. These projects include my current role as Assistant Investigator in Patient Oriented Research at the Feinstein Institute for Medical Research of Northwell Health. I have been involved in numerous research projects and studies on pelvic organ prolapse and urinary incontinence. I have presented numerous abstracts and published peer reviewed articles on pubovaginal slings and synthetic midurethral slings. I have authored two chapters on female pelvic surgery in textbooks. Furthermore, I am currently the Principal Investigator developing a rabbit model for the evaluation of polypropylene and absorbable meshes.

Not only have I personally contributed to the literature for the treatment of pelvic organ prolapse, but I also have been involved in evaluating the quality and content of research presented at meetings and published in journals. I have been a reviewer for the International Urogynecology Journal, Female Pelvic Medicine and Reconstructive Surgery, American Journal of Obstetrics and Gynecology and was an abstract reviewer for the AUGS 2015 Annual Meeting.

My Curriculum Vitae is attached as Exhibit 1.

Clinical Experience:

Throughout my career I have been trained to perform diverse and manifold gynecologic surgeries via the open abdominal route and laparoscopically, including robotic assisted and vaginal procedures. I have performed pelvic reconstructive procedures with a patient's own tissue (native tissue repairs), cadaveric tissue, animal tissue, and synthetic materials.

During my residency I received comprehensive training in general gynecology and obstetrics. I obtained extensive training in repairing complex tears and lacerations that occur during vaginal delivery, and repaired hundreds of episiotomies. I was taught how to manage short and long term complications from episiotomy repairs and damage to the vagina and pelvic floor. During residency I learned the principals of gynecologic surgery, abdominal and vaginal, as well as indications and complications for the various gynecologic surgical procedures. I received extensive teaching, training and experience in abdominal, laparoscopic and vaginal surgery. Although the majority of the pathology appreciated during residency was surgically managed through the open abdominal route.

After I completed residency in 1996 in order to advance my surgical skills as well as to perform meaningful care and research to improve the lives of women, I opted to do a fellowship (additional training) and specialize in Urogynecology, Female Pelvic Medicine and Reconstructive surgery (FPMRS). Back in 1996 Urogynecology was a field in its infancy. There were no structured, organized programs with requirements mandated by an accrediting

body. Furthermore there was no official subspecialty of FPMRS but the fellowship programs resembled apprenticeships.

During my fellowship I studied under Dr. Peter Sand who was one of the early pioneers of Urogynecology. During the 2 years of fellowship I learned the principals of pelvic organ prolapse (POP) and stress urinary incontinence as well as surgical and non-surgical treatment options. I learned how to treat complex pelvic floor disorders including managing and treating the complications that can arise from these procedures.

As was common during the 1990's and early 2000's surgeons and fellowship programs primarily performed pelvic reconstructive surgeries either vaginally or abdominally. My fellowship program and initial exposure to pelvic reconstructive surgery for POP was almost exclusively via the vaginal route. This coupled and complemented well with my residency training which was skewed to the abdominal approach. I still remember and even to this day comment to the fellows that I train, that I only performed 3 abdominal sacral colpopexies during my fellowship. I mention this to my fellows to highlight the importance of continuous learning throughout ones career in order to provide the highest quality of care to our patients.

My education and training in fellowship focused on vaginal native tissue repairs performing vaginal hysterectomy, sacrospinous suspensions and uterosacral suspensions for apical vaginal prolapse and colporrhaphy for cystocele and rectoceles. When I completed fellowship I was an expert vaginal reconstructive surgeon but I subsequently learned and became an expert abdominal and robotic surgeon through hard work and dedication.

I previously mentioned that during my fellowship I only performed few abdominal procedures for POP. Additionally, during the time period of my formal training robotic surgery did not exist, nor did the tension free mid-urethral sling exist. In order to learn these procedures I went to additional courses, as well as operated with surgeons who were skilled in these procedures. Subsequently, I became an expert in both abdominal as well vaginal POP procedures. I

developed the ability to provide the appropriate surgical procedure for the patient rather than find the suitable patient for the surgical procedure I performed. This ability allowed me to become a true expert in the field of FPMRS. During my career I have performed approximately 250 robotic sacral colpopexies, 500 open sacral colpopexies, 1000 uterosacral and high uterosacral suspensions, 300 sacrospinous suspensions, 200 transvaginal mesh procedures, and 3000 midurethral slings.

The reality that I needed to learn surgical procedures after my official training period has driven me to provide this opportunity to other physicians who wish to expand their surgical armamentarium and provide the highest quality of care to the women they treat. To this end, I have taught training sessions, didactic and cadaver labs over the past several years to hundreds of urologists, gynecologists, and FPMRS physicians. I have also have had physicians observe surgical procedures that I perform. Continuous life learning is one of the core competencies that is mandated by the Accreditation Council for Graduate Medical Education. Learning, advancing, and fine tuning surgical knowledge and skills are undoubtedly invaluable, and these labs provide that opportunity. I myself learn something new at each one of these teaching opportunities. Similarly, surgeons are expected to stay current with the medical literature in their field, and especially for the procedures they are performing.

I have had extensive experience in treating complications after gynecologic surgeries, including abdominal sacral colpopexy, native tissue repairs for prolapse, and transvaginal mesh. My first exposure to surgical complications occurred in medical school typically from rotations on the surgical and obstetrics and gynecology services. The majority of the complications observed were a result of everyday surgical procedures performed. I learned early in my career that complications can occur from the most minor procedures and the majority of complications materialize after routine surgical procedures. The adage of the definition of “minor surgery is surgery performed on someone else” was ingrained in me when I was only a medical student.

I received further training in preventing, identifying and treating surgical complications during residency. I learned to evaluate and manage intraoperative and short and long term complications of open abdominal, laparoscopic and vaginal surgery through didactic lectures, reading textbooks and journal articles as well as one-on-one training with attending surgeons.

The bulk of my training in dealing with surgical procedures for pelvic organ prolapse has come from my fellowship training and continuing medical education as a practicing physician. During fellowship and practice I have obtained extensive knowledge and skills in managing complications from abdominal or laparoscopic/robotic sacral colpopexy including but not limited to : bleeding, infection, injury to the bladder, blood vessels, bowel, ureters, and nerves, urinary retention and voiding dysfunction, osteomyelitis, pelvic pain, dyspareunia, exposure/erosion into the vagina, bladder, and bowel, urinary incontinence, and fistula. I have also obtained extensive knowledge and skills in managing complications from native tissue vaginal repairs including but not limited to: bleeding, infection, injury to the bladder, blood vessels, bowel, ureters, and nerves, urinary retention and voiding dysfunction, pelvic pain, dyspareunia, urinary incontinence and fistula. As a practicing surgeon I have also obtained extensive knowledge and skills in managing complications from transvaginal mesh including but not limited to bleeding, infection, injury to the bladder, blood vessels, bowel, ureters, and nerves, urinary retention and voiding dysfunction, pelvic pain, dyspareunia, exposure/erosion into the vagina, bladder, and bowel, urinary incontinence and fistula.

Materials Reviewed:

Throughout my career I have extensively researched, reviewed and contributed to the published medical literature describing the safety and efficacy of POP treatments and procedures, including abdominal and transvaginal mesh.

In preparing this report I have searched and reviewed hundreds of medical and scientific literature regarding the design properties of meshes and the safety of mesh in prolapse repair. In addition to reviewing the materials provided to me, I have performed literature searches in

response to the claims that polypropylene mesh is not reasonably safe for the treatment of POP. Most of the articles I have reviewed in preparation of this report I had already reviewed as part of my due diligence and continuing medical education throughout my career.

I have reviewed the Gynemesh PS and Prolift Instructions for Use, Patient Brochures, and Professional Education materials. A complete set of the materials I reviewed are set forth in my reliance list, attached to my report as Exhibit 2. I reserve the right to supplement my report based on my review of new materials. Additionally, I have reviewed plaintiffs' experts' general reports and the literature and documents they cite in their reports to support their opinions.

Expert Testimony:

Granados, Bethany an infant by Nora v. Moon (2013)

Fees:

My expert fees in this matter are as follows: $650/hour for reviewing cases, working on reports, and meetings; $ 7,000/day for deposition testimony; and $8,000/day for trial testimony.

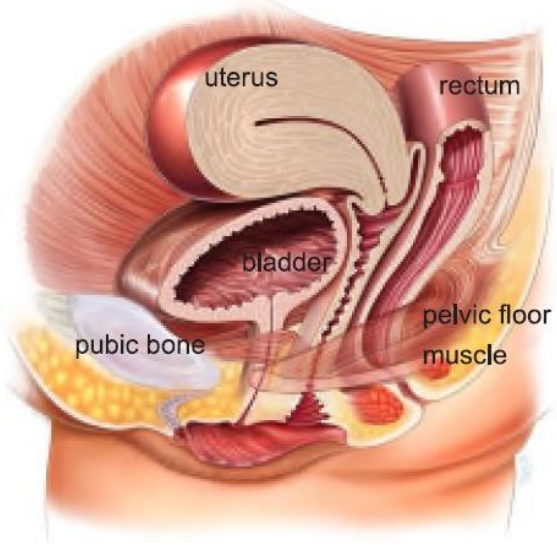
Opinions:

Pelvic organ prolapse (POP) affects a women's quality of life

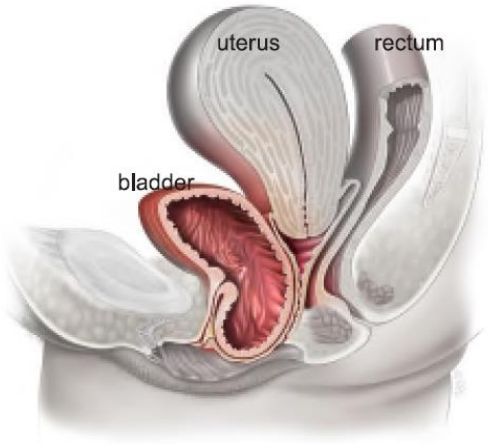
Pelvic organ prolapse (POP) is defined as the decent of the pelvic organs, down and possibly out of the vaginal opening. The vagina can be separated into 3 compartments anterior, posterior, and apical. The bladder rests on the anterior vaginal wall and when the supportive tissue between the bladder and vagina weaken the bladder can descend or bulge into the vagina and is termed a cystocele. Many women and physicians call a cystocele a "dropped bladder". Apical prolapse occurs when the uterus and/or vagina herniates or drops down the vagina. It is important to note here that apical prolapse can occur even after a hysterectomy, and when this occurs small bowel may also herniate into the vagina and this is termed an enterocele. The rectum is located under

the posterior wall of the vagina. When the supportive tissue between the rectum and vagina weaken the rectum may bulge up into and out of the vagina and it is called a rectocele.

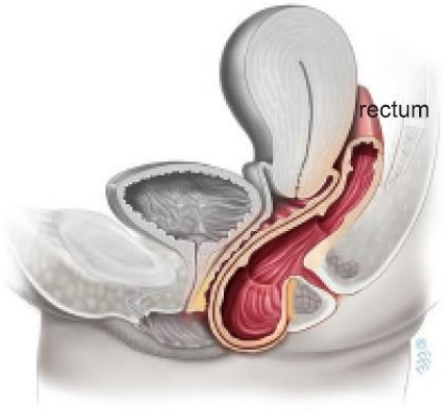
Normal anatomy, no prolapse



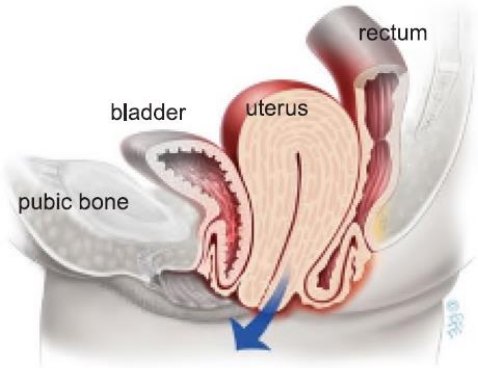
Anterior Compartment prolapse



Posterior Compartment prolapse



Uterine prolapse



Pelvic organ prolapse is seen in 40-60% of women on examination. However, most women are not symptomatic from prolapse. Symptoms of POP include: feeling or seeing a bulge at or past the vaginal opening, feeling of fullness or heaviness in the pelvic region, pulling or aching feeling in the lower abdomen or pelvis, painful or uncomfortable sex, difficulty urinating or having a bowel movement[1].

POP treatment options

Treatment options for POP include no treatment, pelvic muscle exercises, a pessary, or surgical management. Bothersome side effects from pessaries include: vaginal discharge, discomfort, bleeding, and foul smell. Although pessaries have excellent results they need to worn lifelong

and require removing and cleaning on a regular basis. Several visits a year to the physician's office are commonplace for pessary maintenance. Furthermore, a neglected pessary could result in significant morbidity such as fistula into bladder or rectum.

Olsen at al. in (1997) reported that a women had an approximately 11% chance of having surgery for urinary incontinence or pelvic organ prolapse in their lifetime[2]. By 2014, this number had increased to 20% and the risk of undergoing prolapse independently was 14%[3]. In 2006 the average age of women undergoing surgery for POP was 57.3 ± 14.1[4] signifying that a significant proportion of these women are postmenopausal. Approximately 300,000 surgical procedures for prolapse are performed annually in the US.

POP surgical options

Surgery for POP can be either obliterative or reconstructive. Obliterative procedures close or significantly shorten the vaginal canal, are irreversible and sexual intercourse is not possible after. Although obliterative procedures have a high satisfaction rate it is not a viable for many women who therefore opt for reconstruction. Prolapse procedures can be performed abdominally, laparoscopic with and without robotic assistance or through an incision, and vaginally. Reconstruction is also performed with the patient's own tissue or with the use of a synthetic or biologic graft.

Studies across types of surgical procedures have shown decreased success rates in patients with more severe prolapse[5]. Although native tissue repairs have been accepted to have good functional outcomes there are few randomized trials proving reliable and durable long term success rates. For instance, the recent RCT by Barber et al. (2014) for native tissue apical support revealed a 18% failure rate for symptoms of vaginal bulge, 17.5% failure rate of prolapse beyond the hymen and 5.1% retreatment with pessary or surgery and this was only after 2 years[6].

TRANSVAGINAL MESH USE OF GYNEMESH PS AND PROLIFT:

Traditional native tissue repairs vaginal hysterectomy and anterior and posterior colporrhaphy are procedures that are over 100 years old. For the last 5 decades surgeons have been searching for a suitable permanent material to ensure a long lasting result for women with pelvic organ prolapse. The use of a synthetic mesh with Marlex, woven polypropylene, was first described in 1964 by Ferguson[7]. Over 30 years later the use of a synthetic mesh was further popularized by Julian (1996)[8] and Flood (1998) et al[9]. In both of these studies mesh was used to augment or reinforce a traditional native tissue repair or colporrhaphy. In simpler terms after sutures were placed to plicate (pull together) the weakened connective tissue under the bladder the mesh was sutured in below it and the vaginal tissue was closed over the mesh.

Julian (1996) performed the first prospective case control study on transvaginally placed mesh, in 24 patients who had previously failed at least 2 native tissue repairs[8]. Marlex mesh (woven polyester) was used to augment the native tissue repair in half the patients. At 2 years follow up there were no failures in the mesh group as opposed to 4 (33%) in the control group. Two patients had erosion of the mesh through the vaginal tissue and one had granulation tissue. In the abstract he states that this "was associated with common complications related to synthetic mesh." Iglesia (1997) also discusses the commonly known risks associated with mesh repairs based on a review of studies utilizing mesh for incontinence and prolapse repairs[10]. The possibility of transvaginal mesh erosion and exposure was well known and documented clearly prior to it becoming more widespread in the mid 2000's. Despite the known complications surgeons continued to search for a material that can be placed vaginally with long lasting results, less invasive and potential safer alternative to abdominal surgery.

Sacrospinous ligament suspension is one of the common vaginal native tissue procedures performed for apical and vaginal vault prolapse. However it is associated with a high recurrence rate of anterior prolapse. This has been well documented in the literature and a recent RCT revealed an anatomic failure of 19.3% in the anterior compartment 12 months post operatively[11].

With paucity in the literature, in the late 1990'and early 2000's, regarding the use of synthetic materials in gynecological surgery much of the early theories were derived from the hernia literature. Native tissue surgery for POP at that time was reported to have a high anatomic failure rate, and approximately 30% of patients opted for repeat surgery[12]. There was scientific evidence from the hernia literature that primary repairs with synthetic meshes had better long term success rates than a native tissue repair. Based on the high anatomic recurrence rate of POP procedures, at the time, the intention was to reduce the recurrence rate using a synthetic mesh.

Amid (1996) defined 4 distinct mesh groups[13]; Type I - Macroporous >75 μm, Type II – Microporous < 10μm, Type III - Macroporous with microporous component, and Type IV - submicronic pores. 75 microns is the required pore size for fibroblasts, collagen fibers, blood vessels and importantly macrophages which help fend off infection. Due to the specific microflora of the vagina we learned that knitted monofilament meshes performed better than woven and/or multifilament materials. Pore size is integral on how a mesh performs when implanted in the body. Although the Amid Classification is the prevailing criteria in urogynecology, studies have reported that a pore size above 1mm allows for increased flexibility of the mesh and promotes collagen deposition and ingrowth. Coda (2012) proposed a further classification; ultralight ≤35 g/m2, light 35–70 g/m2, standard C 70–140 g/m2, and heavy ≥140 g/m2[14]. Even though this particular classification was not proposed until after the introduction of Prolene PS and Gynemesh PS met the "ideal" requirements for use in prolapse surgery. The pore size of Gynemesh PS is often cited as being 2.4 to 2.5 mm, far larger than both 75 microns and 1 mm. The properties of Gynemesh PS are described in the Gynemesh PS White Paper[15], and are reported throughout the literature (Washington, 2011; Jones 2009)[16].

TABLE 1:
Mesh Characteristics

Characteristic	GYNEMESH PS	PROLENE Mesh	MERSILENE Mesh
Thickness (in)	0.016	0.019	0.010
Unit Weight (mg/cm²)	4.36	7.60	4.22
Porosity (% of total area)	65.6	53.1	62.7
Burst Strength (psi)	115.82	234.33	82.92
Flexibility (mg/cm)	176.71	623.53	17.41
Tear Strength (lb)			
W (knitting machine axis)	4.41	7.32	1.23
C (across machine axis)	2.56	9.03	1.27
Suture Pull-Out (lb)			
W (knitting machine axis)	5.96	11.22	2.27
C (across machine axis)	6.55	13.88	2.06
Tensile Strength (lb)			
W (knitting machine axis)	21.67	50.48	26.37
C (across machine axis)	21.78	42.32	13.39

GYNEMESH PS is designed to be lightweight and soft, so that it conforms to the anatomy and lies flat.

Pelvic reconstructive surgeons in the late 1990's and throughout the 2000's primarily did repairs either vaginally or abdominally, they were experts in one or the other but not commonly both. The training programs in those years were neither well standardized nor certified and were more like apprenticeships. Many of the experts today, myself included, learned surgical procedures from one, and if they were lucky, two surgeons. I was trained as a vaginal surgeon, and as stated prior, I had to learn the advanced techniques of abdominal procedures after my formal training. Vaginal surgeons, observing the success of abdominal procedures with permanent mesh and appreciating the benefits of decreased risks with vaginal surgery, as well as having knowledge of the literature that was available at that time began implanting soft polypropylene mesh vaginally to increase the durability and success rate of the repairs they were performing.

Gynecologists and urologists, who were performing surgery and vaginal native tissue repairs, for prolapse as well stress incontinence procedures, were well aware of the risks of the procedures including pain, dyspareunia, bleeding, infection, and damage to organs. During their residency and training they learned about these complications through didactic lectures, informal discussion with teaching surgeons during surgical procedures and taking care of these patients postoperatively. They gained further knowledge about these risks and how to manage and treat these complications in practice and continuing education.

The early implanters of transvaginal mesh were experts in the field of vaginal surgery. It is incomprehensible to think that the vaginal surgeons who were the early adopters of transvaginal mesh and subsequently who became the teachers of these techniques, to not have known the inherent specific risks of transvaginal mesh placement such as erosion and exposure, as well as the inherent risks of vaginal surgery including dyspareunia and pain, both of which can be transient or chronic, and to not have conveyed these risks to their patients and to the surgeons who they subsequently taught the procedures to. These are basic complications of vaginal surgery that I teach to residents and fellows on a daily basis, are widely discussed in the medical literature, are tested on board exams, and are considered foundational knowledge for vaginal surgeons. The risks of prolapse repairs share the same risks as vaginal mesh repairs, with the exception of mesh erosion, and would therefore be part of the basic set of complications that

were well known and taught. Surgeons do not learn surgical complications such as the potential risk of nerve damage, chronic pelvic pain, persistent dyspareunia, or a risk of suture erosion after traditional prolapse repairs by reading IFUs. Furthermore it is presumed that every OB/GYN as well as urologist who performs prolapse surgery is a "vaginal expert" and would therefore be familiar with these integral risks of vaginal surgery and transvaginal mesh.

Erosion, exposure, dyspareunia, and pain are risks are inherent to pelvic reconstructive surgical procedure as well as to the specific type of mesh used. Erosion and exposure only occur when a foreign body such as a mesh or permanent suture is placed however dyspareunia and pain are intrinsic risks to vaginal and/or pelvic surgery. The risk of dyspareunia and effects on sexual function with a transvaginal synthetic mesh placement were well known and documented in the gynecology and urology literature in the late 1990's[17,18], well before Gynemesh PS and Prolene Soft Mesh were introduced.

For patients, surgeons, and the medical community it is important to develop standardized and reproducible surgical techniques and procedures that can be taught to others and studied over time. Prior to the introduction of the transvaginal mesh kits, vaginal surgeons including myself, were cutting and forming their own pieces of mesh from Prolene Soft Mesh and Gynemesh PS and implanting them transvaginally for pelvic organ prolapse repairs. My colleagues who were performing transvaginal mesh procedures and I, did not view this as experimental since there was precedent through published data on the vaginal placement of permanent synthetic materials in prolapse repairs. The rationale for me was to use permanent mesh for patients who had failed a prior prolapse procedure, or for post hysterectomy patients with prolapse who were poor candidates for or did not desire an abdominal procedure. To reiterate, when surgeons were using flat meshes we did not rely on a manufacturer to educate us on proper patient selection. I have found the professional education materials that Ethicon distributed for Gynemesh PS and Prolift to be helpful, including the professional education slides, surgical videos, surgical technique guides, and Prolift Surgeon's Resource Monograph. Further, I found the adverse reactions listed in the IFUs to be consistent with the complications that I have seen with Gynemesh PS and Prolift in my clinical practice and in the medical literature that are specific to the device.

Throughout my career I have had experience consulting with industry on device design or modification, procedures, surgical complications, instrumentation, and informational content related to IFUs. I have also recorded and been showcased in surgical device educational videos as per the specific IFUs. I taught multiple professional education courses discussing IFUs. Therefore, it was accurate and appropriate for Ethicon to include the following adverse reactions in the initial Prolift IFU:

ADVERSE REACTIONS

- Potential adverse reactions are those typically associated with surgically implantable materials, including infection potentiation, inflammation, adhesion formation, fistula formation, erosion, extrusion and scarring that results in implant contraction.
- Punctures or lacerations of vessels, nerves, bladder, urethra or bowel may occur during GYNECARE PROLIFT Guide passage and may require surgical repair.

Ethicon included additional risks to the IFU in 2009 at the request of the FDA; however, the additional risks were already well known with any pelvic surgery and were not specific to the device:

ADVERSE REACTIONS

- Potential adverse reactions are those typically associated with surgery employing implantable materials of this type, including hematoma, urinary incontinence, urinary retention /obstruction, ureteral obstruction, voiding dysfunction, pain, infection potentiation, wound dehiscence, nerve damage, recurrent prolapse, inflammation, adhesion formation, fistula formation, contracture, scarring, and mesh exposure, erosion, or extrusion.
- Punctures or lacerations of vessels, nerves, bladder, urethra or bowel may occur during GYNECARE PROLIFT' Guide passage and may require surgical repair.

- Potential adverse reactions are those typically associated with pelvic organ prolapse repair procedures, including pelvic pain or pain with intercourse. These may resolve with time.
- Dissection for pelvic floor repair procedures has the potential to impair normal voiding for a variable length of time.

With the development of transvaginal mesh kits there was now a standardized procedure for these repairs with an option for improved durability of the vaginal procedures we were already performing. Sacral colpopexy which uses a synthetic mesh (primarily an Amid Type I polypropylene mesh) was rapidly becoming the gold standard surgical procedure for apical prolapse. Surgeons inherently understood that native tissue repairs would likely not provide suitable long term durable results as confirmed by clinical experience and short-term clinical studies. This became increasingly evident by the more than two fold increase in sacral colpopexy procedures performed in the US from 2010-2012[19] after the FDA released the 2008 and 2011 warnings on transvaginal mesh.

The need for a more durable solution is even more apparent today after Siff and Barber's (2016)[20] review on native tissue prolapse repairs which reported a10-15% risk of prolapse beyond the hymen and 10-20% recurrence of bulge symptoms in short term follow-up at 1-2 years postoperatively. They reported a less than 10% reoperation rate, which is not surprising since patients often do not want to rush back to surgery if the original procedure they underwent didn't even last two years. Therefore, as sacral colpopexy became an acceptable technique for primary prolapse repairs, the rationale for transvaginal mesh was that it could provide similar durability of an abdominal mesh-based repair, but with less morbidity through a vaginal route as opposed to an open abdominal incision, and with an acceptable risk benefit profile depending on the particular patient.

The growth of Female Pelvic Medicine and Reconstructive Surgery as a subspecialty coupled with advances in technology and the transfer of information globally has allowed the medical

community the luxury of learning about complications from surgical procedures more rapidly. The first randomized control study on prolapse was published in 1996 on sacrospinous suspension vs sacral colpopexy [21] which reported an optimal or satisfactory outcome in 67% of patients as opposed to 84% respectively, at a mean of 2.5 years. This early and pivotal study steered prolapse surgery to the more invasive abdominal route with the use of synthetic mesh. Even though surgeons had been performing native tissue anterior colporrhaphies for decades, a randomized controlled trial was not published until 2001, reporting 70% failure in the anterior colporrhaphy group[22].

The following several years saw limited publications of RCT's for prolapse. Roovers in 2004 published a RCT on sacral hysteropexy vs vaginal hysterectomy and showed that reoperation for sacral hysteropexy was considerably higher[23]. Finally, beginning in 2007 the high level evidence began to improve and volume of randomized trials for prolapse began to significantly increase, many of the studies actually involved a transvaginal mesh.

Hiltunen et al. (2007)[24] and Nguyen et al. (2008)[25] performed RCTs and published promising one year results. Nieminen et al. (2010)[26] published a 3 year RCT follow up. Hiltunen compared patients with traditional anterior colporrhaphy alone or reinforced with polypropylene mesh. At one year 38.5% of women in the traditional group and 6.7% in the mesh group experienced a recurrence of the anterior wall prolapse. The exposure rate was 17.3% but the authors comment "[T]he frequency of exposures might have been lower if the mesh had been placed under the fibromuscular layer". Nguyen also compared patients with traditional anterior colporrhaphy alone or reinforced with polypropylene mesh. After one year there was a significant difference in optimal and satisfactory anterior vaginal support between the traditional and mesh groups, 55 % vs. 87% respectively. "Improvement in the prolapse and urinary subscales of the PFDI-20 were greater in the polypropylene mesh repair than the anterior colporrhaphy group". The erosion rate (into the vagina) was 5%. Nieminen reported three year data comparing women who underwent traditional colporrhaphy or reinforced with a tailored polypropylene mesh. The recurrence rate in the mesh group was significantly lower than the colporrhaphy group, 13% vs. 41% respectively. Symptomatically the feeling of a "vaginal bulge" was significantly lower in the mesh group.

There was no difference in sexual function and dyspareunia between the two groups. Shown below is a a chart comparing anatomic cure rates for vaginal mesh versus traditional prolapse procedures. (Jacquetin 2013).[27]

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Table 1 Randomised controlled trials comparing polypropylene mesh with traditional native vaginal tissue repairs

Reference	Total number patients	Follow up (months)	Compartment studied	Anatomic cure mesh (%)	Anatomic cure traditional (%)	*p*
Hiltunen et al. [9]	104	12	Anterior	93	62	<0.04
Sivaslioglu et al. [10]	90	12	Anterior	91	72	<0.05
Nieminen et al. [11]	105	24	Anterior	89	59	<0.05
Nguyen and Burchette [12]	75	12	Anterior	87	55	<0.05
Carey et al. [13]	139	12	Anterior Posterior	81	65.6	0.07
Nieminen et al. [14]	202	36	Anterior	87	59	<0.0001
Withagen et al. [15]	194	12	All	90	55	<0.001
Altman et al. [16]	389	12	Anterior	82	48	0.008
Sokol et al. [17]	65	12	All	38	30	0.45

Prior to 2010 there was also limited data available on the long term success on the standard forms of native tissue repairs for cystocele, rectocele and apical prolapse. Short term data 1-3 years does not shed light on the true long term success rates that patients and surgeons demand and are interested in. Surgeons were forced to provide surgical counseling, provide recommendations, and perform procedures relying on: mostly level B and C published data, physician experience, abstract data at national and international meetings as well as discussion with other surgeons and learning from their experience. Sung et al. (2008) performed a systematic review of prolapse surgery with transvaginal graft and based on the data available were unable to provide guidance on whether or not to use graft materials[28]. Surgeons, including myself, who were implanting transvaginal mesh were attempting to improve the durability of the prolapse surgery without significantly increasing morbidity, understanding and conveying to patients that there was indeed increased risk of mesh erosion or exposure, and based our intentions on this. The benefits of a more durable repair were crucial.

The most recent Cohrane (Maher, 2016)[29] review does indeed reveal superior objective and subjective outcomes at 1-3 year for transvaginal mesh as compared to native tissue in patients who had anterior or multi-compartment failure. It is important to note here that the Anterior

Prolift procedure was not intended to be an apical support procedure and anatomic failures in those patients may have been due to inadequate support of the apical component as approximately 70%-80% of cystoceles are accompanied with apical prolapse. Quality of life and complications, including dyspareunia, were similar between the two groups. The long-term data evaluating quality of life after traditional repairs is not robust. The 2016 Cochrane Review found that "[t]here was no evidence of a difference between the groups in rates of de novo dyspareunia." Additionally, the review noted that recurrence and rates of repeat surgery for prolapse were both lower in the mesh group, although more women in the mesh group required repeat surgery for the combined outcome of prolapse, stress incontinence, or mesh exposure. It is no surprise that using composite a composite group for repeat surgery that includes mesh exposure will be higher in the mesh group. Dietz (2013)[30] reported (grade B evidence) that with regard to the anterior department, "the use of mesh is associated with neither a worsening in sexual function nor an increase in de novo dyspareunia compared with traditional anterior colporrhaphy".

When it comes to mesh procedures we commonly see the majority of complications shortly after the procedures are performed while we do not see the significant benefits of improved symptomology and quality of life for several years after the procedure, as progression of prolapse and failure occurs slowly over time. Numerous studies have noted that complications usually occur within the first 12 months after implant. Iglesia et al. (2013) in her contentious RCT of Prolift vaginal mesh for prolapse reported no new patient occurrences of mesh erosion from 1-3 years and one only patient had an asymptomatic recurrence of exposure at the same location of a mesh revision at 3 years[31]. Interestingly, the suture erosion rate, which was not published in the Iglesia paper, was published in the follow-up study by Sokol (2012)[32] and showed a similar rate of 15% as the 15.6% mesh exposure rate which prematurely halted enrollment in the study.

The significant proportion of reoperations after transvaginal mesh procedures have been for vaginal erosion. Originally, when we started implanting transvaginal mesh the common perception was that all of these erosions symptomatic or not required treatment, and if they

didn't resolve with conservative treatment reoperation was necessary. As a result, a significant number of asymptomatic patients subsequently underwent repeat surgery. As our knowledge and risks of vaginal exposures developed we learned that small and possibly even large mesh exposures are safe to observe and do not need surgical revision.

ABDOMINAL USE OF PROLENE PS & GYNMESH PS:

The road to find the ideal mesh for abdominal sacral colpopexy (ASC) has not been direct either. Surgeons have attempted to use a patient's own tissues (autologous), cadaveric tissue, biologics from other species as well as synthetic materials. Synthetic meshes offer advantages such as consistency, accessibility, and decreased morbidity from not having to harvest a patient's own tissues. A variety of materials have been utilized including Gore-Tex, Teflon, Mersilene and Polypropylene. Cundiff et al. (2008) concluded that Gore-Tex should not be used for sacral colpopexy[33]. The common use of polypropylene for sacral colpopexy did not result from carefully planned prospective studies, but rather, from trial and error and retrospective studies. Ensuing reviews have reported a lower rate of vaginal mesh erosion with polypropylene than compared to the other various synthetic grafts available. Consequently, polypropylene has evolved as the standard material for sacral colpopexy and numerous studies overwhelmingly support its use.

There are limited studies comparing sacral colpopexy to a biologic material and only one study with any type of long term data. Culligan et al. (2011) reported long term (5 year) data of an RCT comparing cadaveric fascia lata vs polypropylene mesh[34]. Objective cure rates were 62% vs 93% respectively, albeit subjectively they report no significant difference between the two groups. FitzGerald et al. (2004) reported a 43% failure rate one year after patients had a sacral colpopexy with donor fascia and 40% of all patients underwent repeat surgery at a median follow up of 17 months[35]. Barber and Maher (2013) in a review of vaginal apical prolapse procedures concluded that ASC with polypropylene mesh had superior outcomes to fascia lata, porcine dermis and small intestine submucosa[36]. Deffieux et al. (2102) issued guidelines from the French College of Obstetrics and Gynecology and recommended not to use silicone-coated polyester, porcine dermis, fascia lata, and polytetrafluorethlene meshes for sacral colpopexy[37].

In the late 1990's and early 2000's surgeons began to commonly use Prolene (polypropylene) mesh abdominally for sacral colpopexy despite not having a specific indication in the IFU for such. Despite this, surgeons understood the inherent risks of using a foreign body from the literature, training and clinical experience. Surgeons were seeking more durable and reproducible results from the procedures they were performing in order to provide a better solution for their patients. Over time, many surgeons in order to try and reduce known mesh complications specific to using a synthetic switched to a lighter weight and softer mesh and started using Prolene Soft Mesh or Gynemesh PS, which became available in 2000 and 2002, respectively.

As with any surgical technique information was continuously acquired regarding short and long term complication rates, which then allowed surgeons to assess the frequency and severity of such complications. With that knowledge gained continuous improvements and refinements were made in the procedure, type of mesh and fixation materials that were used. Immediate short term complications related to the procedure included bleeding, infection, DVT, and damage to other organs. Long-term complications include mesh exposure/erosion, intestinal adhesions and developing small bowel obstruction, chronic pelvic pain, and dyspareunia – all of which are commonly known complications of prolapse surgery with or without mesh (arguably with the exception of mesh exposure).

In 2004, Nygaard et al. in a review of the literature of sacral colpopexy data reported a mesh erosion rate of 3.4% for sacral colpopexy and a success rate 78-100%, 6 months to 3 years postoperatively[38]. In the same cohort of patients the probability of mesh erosion at 7 years was 10.5% (Nygaard et al. 2013)[39]. It is important to note that in this study approximately half of the procedures were performed with woven polyester or expanded polytrafluroethylene, which we know today have higher erosion rates than polypropylene. In 2008, Cundiff et al. reported at 5.1% erosion rate for polypropylene mesh at 2 years follow up[26]. The most recent Cochrane review (2016) reports a mesh exposure of only 3%[40]. Despite the known surgical risks as well as the risk of mesh erosion sacral colpopexy is a standard treatment for POP and considered by an overwhelmingly majority the "gold standard".

Throughout the years pelvic surgeons have been attempting to decrease the known mesh erosion rate with sacral colpopexy. Performing a supracervical hysterectomy rather than a total hysterectomy in patients with uterovaginal prolapse is one technique used. Despite these attempts, mesh erosions still occur and are considered an acceptable risk of the repair. However, it is interesting to note that a mesh exposure from an abdominal sacral colpopexy must be treated differently than that of transvaginal mesh. Erosion from an abdominal sacral colpopexy mesh is significantly more difficult to treat than erosion from a vaginal mesh. Further, a mesh exposure from a sacral colpopexy can result in sacral osteomyelitis, which has been reported multiple times in the literature. Transvaginal mesh does not have this risk as it is attached to soft tissue, extraperitoneally. Consequently, mesh erosion/exposure from abdominal sacral colpopexy should be considered a more serious medical complication which requires operative removal, as compared to an exposure from a transvaginal mesh, which is often asymptomatic, can resolve with estrogen, be managed conservatively, or can be easily excised.

Sacral colpopexy has been accepted by clinicians as having the longest durability and success rates amongst the various POP reconstruction procedures. This need for desired durability of a synthetic mesh is evident by the previously mentioned increase in sacral colpopexy in 2010-2102. There has been only one RCT (Rondini 2014) comparing sacral colpopexy to uterosacral suspension which is the most common apical native tissue repair performed today. After one year the anatomic success rate, defined at least 1cm above hymen, was significantly better for the sacral colpopexy group 100% as opposed to 82.5% for the uterosacral group[41]. The most recent Cochrane review (2016)[33] reports that recurrent prolapse of the anterior, posterior, and apical vaginal compartment is more likely after vaginal procedures.

Incidentally, the abdominal sacral colpopexy in the early to mid-1990's was a procedure associated with the risk of large and life threatening blood loss and was reserved predominantly for patients with recurrent prolapse who failed one or two vaginal native tissue procedures. Many surgeons at that time did not possess the skills to safely perform this procedure, and there are still surgeons today who do not perform it as a primary procedure for uterovaginal prolapse. Despite this, in the mid to late 2000's, sacral colpopexy as a primary repair for apical prolapse

gained in popularity. Presently it is accepted as the gold standard procedure for apical pelvic organ prolapse, nearly universally using a macropourous polypropylene monofilament mesh.

It is important to note here that mesh that is placed abdominally for sacral colpopexy is a different procedure than mesh placed transvaginally. Dr. Daniel Elliott in his general Prolift expert report for the Plaintiffs stated: "Although mesh is used in sacrocolpopexy, there are important distinctions between the two procedures. The amount of mesh used in scarocolpopexy is significantly less than the typically used in the Prolift System and other transvaginal mesh POP repair procedures. The anatomical location of the mesh and the forces applied to the mesh during implantation also differ between the two procedures". In sacral colpopexy, the mesh is "much less likely to experience folding or roping during insertion. In conclusion Elliot states the "risk profile of sacrocolpoexy is superior to that of transvaginal mesh kits for POP". He further states "I only use mesh for POP repair through robotic sacrocolpopexy, as it is not a transvaginal surgery, uses much less mesh, and is associated with significantly less complications than transvaginal surgery". Finally, the FDA is not requiring any additional studies on the placement of abdominal mesh for ASC.

TRANSVAGINAL MESH AND DYSPAREUNIA:

Patients with POP generally have improvement of sexual dysfunction with native tissue repairs as well as with transvaginal mesh surgery. Although many patients show improvement of baseline dyspareunia and sexual dysfunction, there are patients who develop de novo dyspareunia from both native tissue repairs as well as transvaginal mesh.

The question is not if mesh placed vaginally causes dyspareunia, but rather, does it cause painful sex a higher rate than other surgical procedures or the natural progression of aging, and whether or not the benefits outweigh the risks. Several studies have described the prevalence of chronic pelvic pain and dyspareunia in women in the United States: Mathias (1996)[42] reporting 14.7% of women with chronic pelvic pain; Jamieson (1996)[43] reporting 46% of women with persistent dyspareunia and 39% with pelvic pain; Glatt (1990)[44] reporting 33.5% of women with

dyspareunia; Laumann (2004)[45] reporting on various studies showing prevalence of sexual dysfunction in women ranging from 25% to 63%; Latthe (2006)[46] conducted a systematic review for the World Health Organization and reported an incidence of dyspareunia between 8-22%.

Dyspareunia is multifactorial and has multiple etiologies, including but not limited to: vulvodynia, dysmenorrhea, endometriosis, fibroids, pelvic organ prolapse, interstitial cystitis, urgency/frequency syndrome, levator ani syndrome, bowel/bladder incontinence, low back pain, lumbar radiculopathy, sacroiliac joint dysfunction, coccydynia, hip disorders, anxiety, depression, and history of abuse (Eickmeyer 2016)[47]. For the purpose of this report I will focus primarily on menopause and injury to the vagina as causes for dyspareunia.

Dyspareunia has been a long term known complication of vaginal surgery (Francis 1961)[48]. Episiotomy performed at the time of vaginal delivery is the most common performed procedure by an overwhelming majority of obstetricians and gynecologists. It is considered minor surgery and is so commonly performed, important, and pervasive in clinical practice ACOG produced a clinical monograph in 2007[49]. Pain and dyspareunia are listed as complications of episiotomy and can occur in almost 40% of women receiving an episiotomy. It is well established that a routine episiotomy can cause dyspareunia. Persistence of dyspareunia can persist after delivery and can be present at 6 months or longer in 11% of women who had an episiotomy or perineal laceration (Buhling KJ et al. 2006)[50].

Residents in OB/GYN as well as urology are instructed in the possibility of dyspareunia developing from vaginal surgery throughout their training. This is accomplished through didactic lectures as well as clinical training. Complications from mesh placed vaginally have been well documented, prior to the introduction of Gynemesh PS and Prolift, in both the urologic and gynecologic literature and textbooks. Furthermore, early experience in 1998 from complications from a woven polyester sling, which was well publicized and documented in the literature, ensured that urologists and gynecologists were fully aware of the risks of erosion, dyspareunia and vaginal pain from the placement of synthetic materials vaginally.

Menopause and vaginal atrophy that consequently occurs is one of the main contributors to dyspareunia in postmenopausal women. Approximately, 21.5% to 29% of postmenopausal women experience dyspareunia[51]. Although the rate of dyspareunia seems to decrease as women get older, this is likely attributed declining sexual activity in older women as opposed to dyspareunia diminishing. Since a significant proportion of women who undergo surgery for POP are menopausal and continue to age, as time goes on, it is not surprising that a substantial percentage of women would have dyspareunia from atrophy alone and will likely have a natural declining rate of sexual activity as they age.

Studies have reported significant dyspareunia developing after native tissue prolapse repairs. Komesu et al. (2007)[52] reported an increased trend of dyspareunia in patients undergoing poster repair. Abramov et al. (2005) reported a significant increase in dyspareunia rates to17% from 8%, in a retrospective review of two types of native tissue posterior repairs[53]. It is noteworthy to add, that none of the patients in this group underwent levator plication (a type of vaginal surgery) which is a well-known direct cause of dyspareunia. Weber et al. (2000) reported de novo dyspareunia occurring in 26% of women after posterior colporrhaphy[54]. Jha and Gray (2014) performed a meta-analysis and systemic review on patients who underwent an anterior and/or posterior native tissue repair and sexual function[55]. They reported an 18% worsening of dyspareunia postoperatively with a 4% de novo rate.

When considering procedures to compare dyspareunia rates, native tissue sacrospinous suspension is the most similar to Prolift and the transvaginal mesh procedures that are performed today. Current literature on sacrospinous suspension is sparse as it is not as commonly performed today, as uterosacral suspension has become more predominant. Maher et al. (2004) reported a 7% dyspareunia rate 2 years after sacrospinous suspension[56]. Colombo and Milani (1998) reported a 17% incidence of dyspareunia at least 4 years after a sacrospinous suspension and vaginal hysterectomy[57]. Paraisso et al. (1996) reported a 16% dyspareunia rate and 10% had new onset complaints of sexual dysfunction, at a mean of 73.6 months after sacrospinous ligament suspension[58].

Sacral colpopexy and uterosacral suspension, most commonly, are intraperitoneal procedures and therefore carry added morbidity from such. Silva et al. (2006) reported a 20.6% de novo dyspareunia rate 5 years after uterosacral suspension[59]. Colombo et al. (1998) in a retrospective case control study, at least 4 years postoperatively, reported a 17% rate of dyspareunia following sacrospinous ligament suspension and 25% following modified McCall culdoplasty[60].

Nieminen et al. (2008) performed an RCT on anterior native tissue repair and polypropylene mesh and reported on sexual function 2 years postoperatively[61]. There was no significant difference in sexual function scores at follow up. However, dyspareunia was significantly lower in the mesh group. In the native tissue group 13% of patients reported the vagina was too or slightly too tight for intercourse as opposed to 8% in the mesh group. Carey (2009) performed an RCT in patients undergoing anterior and posterior repair with and without mesh augmentation using Gynemesh PS. It is noteworthy to highlight that the patients in the mesh group had mesh placed in both the anterior and posterior compartments. At 12 months follow up de novo dyspareunia developed in 16.7% of sexually active women in the mesh group and 15.2% in the no mesh group[62]. Despite this there was an improvement in sexual function based on QOL in both groups.

Lowman (2008) reported a 16.7% rate of de novo dyspareunia in patients who underwent a Prolift procedure[63]. A substantial majority of the patients (94.6%) had mesh placed in the posterior vaginal compartment. As stated prior native tissue posterior repair has a significant risk of developing de novo dyspareunia therefore when taking this into consideration it seems that the 16.7% rate is consistent with the native tissue studies. It is notable to add that Lowman reported on the 83% of women who responded and developed de novo dyspareunia would choose to undergo the surgery again.

TABLE 4
De novo dyspareunia after prolapse surgery

Dyspareunia	ASC N = 224 (148)[a] Handa et al[21]	SSLF N = 287 (106)[a] Maher et al[6]	USS N = 110 (34)[a] Silva et al[27]	APR N = 165 (81)[a] Weber et al[18]	Prolift N = 129 (57)[a]
Baseline (preop) dyspareunia (%)	40.5 (60/148)	Unknown	20.6 (7/34)	8.0 (6/81)	36.8 (21/57)
De novo (postop) dyspareunia (%)	14.5 (11/76)	36.1 (22/61)	25.9 (7/27)	19.0 (14/75)	16.7 (6/36)

[a] Number sexually active preop.

Lowman. Does the Prolift system cause dyspareunia? Am J Obstet Gynecol 2008.

Withagen et al. (2011) published 12 month follow up of an RCT of Prolift placed anteriorly, posteriorly or both compared to native tissue[64]. They reported an overall decrease in dyspareunia in both groups. De novo dyspareunia was reported in 8% of the mesh group and 10% in the native tissue group. Seven year follow up data was presented by Damoiseaux et al. (2015) in abstract form and reported 10% de novo dyspareunia rate in the mesh group and 12% in the no mesh group. There was no difference in overall rates of dyspareunia as well between the 2 groups[65].

Altman et al. (2011) performed an RCT on anterior Prolift mesh vs anterior colporrhaphy. At 12 months dyspareunia was reported in 2% of woman in the native tissue group and 7.3% in the Prolift group. However, they did not report on the de novo dyspareunia rate and PISQ rates at 12 months were similar between the 2 groups[66].

Iglesia's et al. (2013) RCT reported 1 year functional outcomes of Prolift vaginal mesh vs native tissue repair in patients with apical and anterior with and without posterior prolapse and reported a 9.1% de novo dyspareunia rate in the mesh group vs 21.4% in the native tissue group[67]. Additionally, both groups had a statistically significant decrease in postoperative vaginal diameter and length however there was no significant difference between the two groups.

Several review studies have investigated dyspareunia and sexual function in patients undergoing transvaginal mash compared to native tissue. Dietz and Maher (2013) specifically reviewed the literature on pelvic organ prolapse and sexual function. There was not enough evidence for them

to conclude that there was no difference in de novo dyspareunia, post-operative dyspareunia and PISQ scores when comparing transvaginal mesh in the anterior compartment to traditional colporrhaphy[68]. Deffieux et al. (2012) reported a 14% de novo dyspareunia rate after placement of transvaginal mesh which is comparable to native tissue repairs[15]. They recommended that patients be informed of the risk of dyspareunia notwithstanding the route of surgery, native tissue or mesh. The most recent Cochrane review (2016) reported no difference in de novo dyspareunia rates when comparing transvaginal mesh to native tissue repairs. Additionally there was no difference between the two groups in prolapse specific sexual function questionnaire scores[23].

Once again it is important to recognize that dyspareunia resolves in more women who have prolapse surgery with or without mesh than those that who develop it after surgery. However, dyspareunia occurring with vaginal surgery is so ubiquitous that any physician performing these procedures is knowledgeable in such and would or should have informed their patients during the consenting process.

There is no doubting that native tissue repairs as well as transvaginal mesh procedures, Prolift and Gynemesh PS included, can cause dyspareunia, intuitively we may even reason that a transvaginal mesh procedure may increase this risk; however, the current data does not substantiate such. Surgeons who perform vaginal reconstructive surgery are aware of the dyspareunia risks based on the data, training, and continued learning. It is our duty as surgeons to convey this information to our patients as it becomes available, discuss these risks and benefits, and individualize them for each unique patient. Surgeons are taught to practice evidence-based medicine, which requires that they review the medical literature to assess the frequency and severity of complications, especially for the procedures they perform.

ABDOMINAL MESH AND DYSPAREUNIA:

The majority of people report improvement in sexual dysfunction postoperatively after sacral colpopexy. Kuhn et al. [69] reported on sexual function in women 2 years after sacral colpopexy in women who had a post hysterectomy vaginal vault prolapse. None of the patients developed de

novo dyspareunia and there was a significant improvement in sexual desire, arousal, lubrication, satisfaction, and pain. There is extremely limited data on the development of de novo dyspareunia after sacral colpopexy attesting to the scarcity of it occurring. A recent Cochrane review (2016) was unable to report on the rate of de novo dyspareunia. However the review revealed that dyspareunia rates may be higher for vaginal native tissue repairs than sacral colpopexy[70].

Maher et al. (2004) performed an RCT comparing sacral colpopexy to sacrospinous suspension and reported 2 year follow up. Preoperative dyspareunia resolved in 56% of women in the abdominal group and 43% in the vaginal group. Dyspareunia developed postoperatively in 5.7% women in the abdominal group and 8.3% women in the vaginal group[43].

Handa (2007) reported that 14.5% women developed de novo dyspareunia one year after sacrocolpopexy with polypropylene mesh; however 58% reported resolution of their dyspareunia[71]. When comparing sacral colpopexy with a biologic material, porcine dermis, to polypropylene mesh Salamon (2014) reported no significant difference in de novo dyspareunia rates between the two, 3.5% vs 5.3% respectively at one year postoperatively[72].

Today the majority of sacral colpopexies are performed laparoscopically with or without robotic assistance. Ganatra et al. (2009) performed a literature review of laparoscopic sacral colpopexy[73]. Mean follow up was 25 months there was a 6.2% prolapse reoperation rate, and a 2.7% mesh erosion rate. Postoperative sexual dysfunction was reported in 7.8% of women.

Sacral colpopexy, however, seems to have an overall lower rate of dyspareunia than vaginal procedures. The most recent Cochrane review (2016) on apical prolapse surgery reports that the data suggests that the relative risk of dyspareunia is 2.53 (CI 1.17 to 5.5) higher for vaginal procedures than sacral colpopexy[57]. Bensen et al. (1996)[5] reported a 58% rate of postoperative dyspareunia after bilateral sacrospinous suspension and none after sacral colpopexy.

Clinically, because sacral colpopexy does not alter the vaginal framework by shortening, or cause significant scarring within the vagina, we expect it to cause less dyspareunia than vaginal procedures. Sacral colpopexy maintaining vaginal length is seen clinically and was established over 20 years ago when compared to sacrospinous suspension by Given et al. (1993)[74]. To this end, sacral colpopexy is the recommended apical surgical procedure for women with prolapse who have a shortened and/or narrowed vagina from prior surgeries.

TRANSVAGINAL MESH AND PAIN:

Developing chronic pain is a commonly known risk of every surgical procedure. It can develop from excessive scarring and increased tension on tissue or nerve entrapment. The hernia literature reports a 10-12% incidence of moderate to severe chronic pain after hernia repair[75]. The data specifically assessing postoperative chronic vaginal and pelvic pain in prolapse surgery is sparse.

Sacrospinous suspension has been known to cause pelvic pain. Damage to the pudendal nerve with subsequent pudendal neuropathy is a well-known debilitating risk of the procedure and if discovered early on necessitates removal of the offending sutures. However pain other than pudenal nerve pain has been described. Unger and Walters (2014) reported a 15.3% rate of gluteal or posterior thigh pain at 6 weeks after a sacrospinous ligament suspension[76]. More profoundly Barber et al. (2104) in the OPTIMAL randomized trial, which compared uterosacral suspension to sacrospinous suspension, reported persistent pain occurring in 4.3% of the patients after sacrospinous suspension, "highlighting the need to provide preoperative counseling to patients about this potential risk"[77].

Altman et al. (2011) performed an RCT on Anterior Prolift mesh vs anterior colporrhaphy. At 12 months they reported that only 1 (0.5%) patient in the mesh group described severe pelvic pain. Deffieux et al. (2013) in a review reported a 4-11% rate of vaginal pain developing after mesh placement depending on the definition used. This is consistent with the pain rate reported in the native tissue OPTIMAL trial[15]. Landsheere et al. (2011) performed a retrospective review on

524 patients who underwent a Prolift repair at 3 year follow-up and 87% of identified patients were included in the analysis. Four (0.8%) patients required wide mesh excision, 2 for symptomatic mesh retraction, presumably for pain, and 2 for rectal compression[78].

Maher (2013) on a review of anterior vaginal compartment surgery reported that no patient who had mesh placed in the anterior vaginal compartment in 8 trials, 533 patients, suffered surgical intervention for dyspareunia or vaginal pain[79]. In the recent 2016 Cochrane review on transvaginal mesh compared with native tissue repair the authors comment in the discussion on transvaginal mesh that "surgery for vaginal pain or dyspareunia was barely mentioned"[80].

Dandolu et al. (2016) performed a database search to quantify the extent of complications for apical prolapse repair with TVM use compared with abdominal or laparoscopic sacralcolpopexy as well as to native tissue repairs. They reviewed the data on large cohort of individuals in the US that had apical prolapse surgeries during a minimum 2-year follow-up. An associated diagnosis of pelvic pain during follow up visit was reported less for transvaginal mesh than native tissue repairs at 16.4% and 22.0% respectively[81]. Several RCTs comparing Gynemesh PS and Prolift to traditional prolapse repairs demonstrated no statistically significant difference in vaginal length or contraction, de novo dyspareunia, sexual function, or pelvic pain (Carey, 2009[60]; Withagen, 2011[62]; Altman, 2011[64]; Sokol, 2012[65]; Halaska, 2012[11]; Svabik, 2014[82]; Da Silviera, 2014[83]).

ABDOMINAL MESH AND PAIN:

Unfortunately, any type of surgery involves risk of developing chronic pain. The more invasive and/or extensive the procedure is the greater the risk of developing chronic pain. Hysterectomy is one of the most common procedures in the United States and can be a cause of chronic pelvic pain. As with any type of surgery scar tissue forms and intrabdominal adhesions can occur with hysterectomy. Although pelvic pain is commonly present before and may be an indication for hysterectomy de novo chronic pain can develop from hysterectomy independently. Brandsborg et al. (2007) reported that 31.9% of women had chronic pain and 14.9% developed de novo chronic

pain 1 year after surgery[84]. Furthermore, there was no difference in chronic pain between vaginal hysterectomy and abdominal hysterectomy. By contrast, Abdelmonem (2010) reported 5% de novo dyspareunia after total abdominal hysterectomy and 20% de novo dyspareunia after vaginal hysterectomy, with more vaginal shortening in the vaginal group[85]. Theunissen et al. reported 2.2% de novo incidence of developing chronic post-surgical pain 3 months after hysterectomy[86].

The majority of the studies on uterosacral suspension do not assess for persistent long term postoperative pain. However it has been established that uterosacral suspension can cause damage to sacral nerve roots, likely through suture entrapment, causing sensory neuropathy. Symptoms may include some or all of the following: de novo buttock, perineal or lower extremity pain, numbness, and weakness. Flynn et al. (2006) reported a 3.8% incidence of sensory neuropathy after uterosacral suspension[87]. Prompt suture removal shortly after surgery usually alleviates the pain however residual symptoms may persist[88].

Stepanian et al. (2008) reported a 1.2% rate of pain at the vaginal apex, at a median time of 12 months follow-up, in patients who underwent laparoscopic sacral colpopexy[89]. Diwadadkar (2009) in a review of complication and reoperation rates for apical prolapse surgery reported a pain complication rate of 2.3%[90]. In the previously mentioned study by Dandolu et al. (2016) an associated diagnosis of pelvic pain during 2 year follow up was seen at similar rates after native tissue repairs and sacral colpopexy, 22.0% and 22.2% respectively[68]. These rates of postoperative pain after sacral colopopexy are comparable to other intrabdominal procedures and are well known to pelvic surgeons.

TRANSVAGINAL MESH AND QUALITY OF LIFE:

In the late 2000's we began defining surgical success for prolapse procedures based not only on anatomic outcomes but on subjective patient perception of success and quality of life outcomes. Up until that time, surgeons were strictly basing surgical success on anatomical outcomes. Since POP is a not a life threatening, but rather a quality of life disorder, this progression made sense to evaluate success from the patient standpoint clinically as well as in research studies on POP.

Although extremely beneficial, this new definition, which was more clinically relevant, altered the landscape of how surgeons gauged success as anatomic failure usually precedes symptomatic quality of life affects from POP.

In 2009 Barber et al. for the Pelvic Floor disorders network redefined the way we asses surgical success for POP and as a result altered what was considered a surgical failure. They recommended: 1) any definition surgical success for POP should include the absence of bulge symptoms in addition to anatomic criteria and the absence of re-treatment and 2) using the hymen as threshold for anatomic seems a reasonable and defensible approach[91]. However, it is important to remember that over 90% of patients who have prolapse to the introitus and beyond will persist or progress over time[92]. Prior to this redefinition many studies used stricter anatomic definitions of success. Suddenly patients who were previously classified as surgical failures now were not considered as such and conversely were considered successful.

This was clearly evident when Chmielewski et al. (2011) reanalyzed data originally published in 2001 on anterior colporrhaphy success rates. Success in the original study was based on the stricter definition of success and reported a 54-70% failure rate[93] however with the newer definition the anatomic failure rate was 11% and symptomatic failure was only 5%[94]. These findings substantiated the difference in success rates when using the updated criteria, although it should be noted that this study was limited by a lack of validated pelvic floor symptom or quality of life questionnaires and if all patients who were lost to follow-up were counted as failures, then the success rate using the new criteria would be 62%. The same is true for the French TVM group's prospective data which did not meet Ethicon's original stringent statistical endpoint (failure rate greater than the upper limit 20% confidence interval)[95]. Even though the initial French TVM study did not meet the statistical goal, the results were overwhelmingly seen as an improvement over native tissue repairs, and patients reported high satisfaction rates, even those who experienced a mesh exposure.

Results and Conclusions: The primary effectiveness variable was recurrence of prolapse at 12 months post-procedure (failure of procedure), with failure being defined as a prolapse of ICS Stage II or more or a surgical re-intervention. The results show a failure rate at 12 months of 18.4% with a 90% CI of 11.9-26.6. Thus the study did not meet the pre-defined criteria of a failure rate of less than 20% (upper limit of 90% CI). Of the 16 failures there was only one patient with a prolapse of ICS Stage III; fifteen patients had prolapse of ICS Stage II. In 10 of the Stage II patients, the leading edge of the prolapse was inside the introitus.

The secondary effectiveness parameters show a failure rate at 6 months of 12.6% (90% CI: 7.3, 20.1). Other secondary effectiveness parameters show a reduction in the number of patients reporting sexual activity limited by prolapse at 12 months compared with baseline (29 [32.2%] *vs* 6 [6.9%]). The incidence of dyspareunia in those patients who were sexually active was 4/61 (7%) at baseline, 8/42 (20%) at 6 months and 3/40 (8%) at 12 months (Tables 14.2.8.2 and 14.2.4.1). One patient (3004) was reported as having dyspareunia at baseline but was not sexually active due to prolapse. The 3 cases of dyspareunia at 12 months were all new onset. Dyspareunia was resolved at 12 months in the 5 patients who reported the condition at baseline.

By comparison, Jacquetin (2013) reported the results from the French TVM 5 year follow-up, with 91% of patients available at follow-up, using the newly adopted criteria for success[96]. The results showed the following:

> *A composite criterion of success defined as: leading edge above the hymen (<0) and no bulge symptoms and no reintervention for prolapse was met by 90 %, 88% and 84%at the 1-, 3-, and 5-year endpoints respectively. Quality of life improvement was sustained over the 5 years. Over the 5-year follow-up period, a total of only 4 patients (5 %) required re-intervention for prolapse, while a total of 14 patients (16 %) experienced mesh exposure for which 8 resections needed to be performed. Seven exposures were still ongoing at the 5-year endpoint, all asymptomatic. Only 33 out of 61 (54 %) sexually active patients at baseline remained so at 5 years. De novo dyspareunia was reported by 10 %, but no new cases at the 5-year endpoint. One patient reported de novo unprovoked mild pelvic pain at 5 years, 5 reported pains during pelvic examination only.*

Subsequently surgical success definition began to include the triad of objective and subjective data as well as quality of life questionnaires. This progression and redefinition of success is a testament to the numerous research studies that were being performed at that time as well the dedication of physicians and researchers. The conclusions of how to evaluate surgical success evolved over time, as did our understanding of the surgical procedures success rates and patient expectations and outcomes. Nevertheless these changes in definitions altered the way patients were informed and how physicians perceived surgical success. The criteria for gauging surgical success radically changed in 2011.

Iglesia et al. (2013) reported 1 year functional outcomes, of a RCT, on Prolift vaginal mesh vs native tissue repair in patients with apical and anterior with and without posterior prolapse. Despite stopping the study prematurely both groups had a statistically significant improvement in almost all QOL measurements which did not differ between the two groups[25]. Functional improvement persisted at 3 year follow up[11].

Maher et al. (2011) in a RCT comparing the total Prolift TVM procedure to laparoscopic sacral colpopexy reported significant improvement in symptom severity and QOL scores in both groups. There was no significant difference in the pre- and postoperative quality of life changes between the groups[97]. Meyer et al. (2016) reported a minimum of 5 year follow up after Prolift mesh placement. Significant improvement was seen on QOL scores and 84% were somewhat or completely satisfied[98]. Heinonen et al. (2016) performed a retrospective analysis on patients who underwent Prolift mesh procedures in the anterior or posterior compartments or both. Median follow up was 7 years, 82.6% of patients were included in the study and 80.1% of women were satisfied with the surgery[99]. Interestingly, patients who required additional surgery due prolapse reoperation or those with mesh complications were equally satisfied.

Maher (2013)[32] reviewed predominantly short to midterm, 1-3 years, outcomes on surgery in the anterior compartment with and without mesh and reported consistent evidence indicating superior objective and subjective outcomes with mesh. However, there was no difference in

functional life questionnaires. In a recent Cochrane review (2016) on transvaginal mesh and native tissue repairs for prolapse, effects on quality of life based on 1-2 year review found no difference between the two groups. Despite this they concluded that the effect on quality of life was indeterminate, due to low quality of evidence. However, recurrent prolapse and awareness of prolapse was less likely with mesh at 1-3 years[33].

Progression of prolapse occurs slowly over time. Bradley et al. (2007) reported that over 3 years postmenopausal women are more likely to progress or develop new prolapse. However during the study only 5 (8.5%) of women progressed enough that they opted for treatment, 4 with a pessary and 1 with surgery. The authors concluded that their data suggested that clinicians can reassure women with prolapse that the likelihood of significant progression is low over a 1-3 year period[100]. Therefore, adequate assessment and determinants of success for POP surgery should be at least 3 years.

Overwhelmingly, studies have shown an improvement in QOL with transvaginal mesh procedures. However, since progression of POP occurs slowly over time it is unlikely that we will see a difference in QOL indicators in native repairs vs transvaginal mesh procedures in the short term, 1-3 years. Longer term studies 3-5-7 years will be necessary to truly determine the durability of the repairs and their effect on QOL.

ABDOMINAL MESH AND QUALITY OF LIFE:

Sacral colpopexy is considered the gold standard for apical vaginal prolapse due its durability, anatomic and functional outcomes, and improvements in QOL. Today, the majority of sacral colpopexies are performed in a minimally invasive fashion either laparoscopically or robotic assisted.

Maher et al. (2004) performed an RCT comparing abdominal sacral colpopexy, using Prolene mesh, to sacrospinous suspension. In the sacral colpopexy group, at a mean of 2 years there were

significant improvements in the Short Urinary Distress Inventory, Short Impact Incontinence Questionnaire, and Short Form-36 Health Survey[101].

Maher et al. (2011) performed an RCT comparing laparoscopic sacral colpopexy, using wide pore Prolene mesh, to transvaginal Prolift mesh. At 2 years here was a significant improvement in symptom severity and quality of life scores using patient administered validated questionnaires, the Australian Pelvic Floor Questionnaire and Kings College Pelvic Organ Prolapse quality of life, in both groups postoperatively as compared to preoperatively. Additionally, there was no significant difference in postoperative quality of life changes between the 2 groups[102].

Pariaso et al. (2011) reported a sacral colpopexy RCT using Gynemesh PS comparing the laparascopic to the robotic technique. They reported significant improvement in quality of life indicators including, PFDI-20 and PFIQ, for both groups with no difference between the groups[103].

Kenton et al. (2106) reported 1 year data in a RCT comparing robotic to laparoscopic hysterectomy. QOL data collected included the Pelvic Floor Distress Inventory (PFDI), Pelvic Floor Impact Questionnaire (PFIQ), Pelvic Organ Prolapse/Incontinence Sexual Questionnaire and Patient Global Impression of Improvement (PGI-I). Both groups had significant improvement in all QOL and symptom measures and there was no difference between the two groups[104].

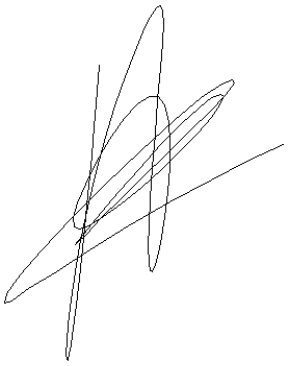
CONCLUSIONS:

Clinically, patient expectations are more demanding than in the majority of studies that exist even today. It is difficult to compress 20 years of experience into a report such as this, and considerably more challenging into a 25 minute preoperative consultation with a patient. Patients expect surgical repairs to last a lifetime, albeit they generally understand that there is no lifetime guarantee. In the US the expected life expectancy of a 50, 60, and 70 year old female is

another 29.6, 21.5, and 14.4 years respectively[105]. We must counsel our patients on the best available data we have at the present. We must use products and techniques which are currently available to achieve an acceptable risk benefit profile to the patient and society. To that end, presently to the best of our knowledge as well as the clinical data, polypropylene is the preferred material to be used in both transabdominal and transvaginal surgical procedures for pelvic organ prolapse.

While the definition of success changed over the years for prolapse surgical procedures so has the understanding of complications from native tissue procedures as well as synthetic mesh surgery. Similarly, as recurrent prolapse in an asymptomatic patient does need treatment and can still be considered a treatment success asymptomatic vaginal mesh erosion does not mandate surgical intervention. When we first began performing transvaginal mesh procedures we treated every patient surgically if there was no resolution with conservative management for mesh exposure. Today, we have gained knowledge and experience that patients with a small and even large asymptomatic mesh exposure do not require treatment if they are asymptomatic, and can be observed. Looking back at the early papers and mesh exposures it is likely applying this knowledge and understanding the reoperation rates in transvaginal mesh groups would be considerably less. I agree with the criticisms and points raised in the 2012 Time to Rethink article in response to the FDA's 2011 safety communication[106].

Despite some of the setbacks that have occurred with transvaginal mesh I am confident that with the present knowledge and materials available, surgeons will continue to implant polypropylene mesh vaginally to the benefit of their patients. As physicians and specialists treating women with POP, we must commit to continued learning, observation, post market surveillance and performing randomized controlled studies to prove the safety and efficacy of native tissue repairs as well synthetic materials.



Signed: _____

Harvey Winkler, MD

Date: February 5, 2017

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